

REMARKS

Claims 57-82 are pending in the application. Claims 65 and 72-82 are withdrawn from consideration. Claims 57-64 and 66-71 are under consideration.

Claims 57-64 and 66-71 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 66-67 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 57-64 and 66-71 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 97/48397 in view of Hoskin et al (British Journal of Cancer, 1997, vol. 76, pages 260-263). Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over WO 97/48397 in view of Olsson et al (British Journal of Cancer, 1996, vol. 74, pages 368-373). Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over WO 97/48397 in view of Pero (USP No. 5,340,565).

Applicants have amended the claims by deleting the term "or ester thereof" from claims 57 and 66. In addition, claim 66 has been amended by incorporating therein the compounds of Formula II-Vb. In addition to be consistent therewith, applicants have amended claim 63.

No new matter has been added in the specification. Moreover, as described hereinbelow, the amendment to the claims are not on account of the patentability issues raised in the Office Action.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 57-64 and 66-71 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action

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alleges that the instant claims recite "a compound having vitamin PP activity or an ester thereof." It is further alleged that the specification does not provide sufficient written support describing the esters for compounds having vitamin PP activity.

Applicants respectfully disagree with the rationale provided in the Office Action in support of the rejection. Contrary to the allegations in the Office Action, there is support for the language in the specification. Attention is directed to page 15, line 7, wherein one of the elements is listed in:

"b. at least one compound having vitamin PP activity or an **ester** thereof which is selected from the group consisting of compounds of Formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va and Vb." (emphasis added)

Thus, there is descriptive support in the specification for the language "ester thereof." Consequently, the rejection of claims 57-64 and 66-71 under 35 U.S.C. §112 is obviated.

However, applicants have amended the claims because the language "ester thereof" is superfluous. The language of "at least one compound having vitamin PP activity or an ester thereof" immediately followed by being selected from the "group" refers to the ester being within the compounds of Formula of II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va and Vb. Therefore, the term ester thereof does not add anything to the definition of the compound having vitamin PP activity. Thus the scope of the subject matter in claim 57 has not been narrowed by this amendment. Further, the amendment to Claim 66 makes explicit that which was implicit, that is, claim 66 specifically recites that the compounds having vitamin PP activity are selected from compounds of Formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, V, Va and Vb.

Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph is obviated and that it should be withdrawn.

The Office Action also rejected claims 66-67 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action alleges that claims 66-67 reciting the phrase "or an ester thereof" is not adequately supported by the specification.

Applicants respectfully disagree with the rationale supporting the rejection and incorporate by reference the comments given hereinabove with respect to the first rejection under 35 U.S.C. § 112. As indicated above, claim 66 has been amended by deleting the phrase "or an ester thereof." Claim 66 was further amended by the addition of language reciting the compounds of formulae II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va and Vb. As indicated hereinabove, claim 66 made explicit that which was implicit.

It is respectfully submitted that this amendment overcomes this rejection.

Accordingly, the Applicants respectfully request that these rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over WO 97/48397 ("WO '397") (Published December 24, 1997) in view of Hoskin et al (British Journal of Cancer, 1997, vol. 76, pages 260-263) ("Hoskin"). The Office Action alleges that WO '397 allegedly discloses compounds of Formula I encompassed by the instant claims. More specifically, the Office Action alleges that it

discloses pharmaceutical compositions comprising a compound of Formula (I), e.g., N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide. However, it admits that WO '397 does not disclose a compound of Formula I with a compound having vitamin PP activity, e.g., a compound of Formulae II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va and Vb. According to the Office Action, Hoskin discloses the instantly elected nicotinamide, which is a compound having vitamin PP activity.

According to the Office Action, Hoskin teaches administering nicotinamide individually and combined with carbogen to patients having bladder cancer undergoing radiation therapy. The Office Action further asserts that clinical results show that carbogen and nicotinamide may improve the results of daily fractionated radiotherapy in bladder cancer.

The Office Action further alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising a compound of Formula (I) as taught in WO '397 and nicotinamide as taught in Hoskin. The Office Action alleges that motivation for combining of the references is described in WO '397, referring to an alleged suggestion that the combinations of compounds of Formula (I) with other chemotherapeutic agents (page 204) as well as with radiotherapy, hyperthermia, or immunotherapy (pages 204 and 206).

Applicants respectfully disagree that Hoskin provides any motivation to persons of ordinary skill in the art of combining the teachings of Hoskin with WO '397 to arrive at the claimed composition. The Office Action apparently concedes that WO '397 does not teach a compound of Formula I in combination with a vitamin PP compound.

Nonetheless, the Office Action alleges that motivation to combine Hoskin with WO'397 is provided in Hoskin's alleged teaching that co-administering carbogen and nicotinamide have been used to enhance the efficacy of radiation therapy.

Applicants respectfully disagree with the rationale set forth in the Office Action. Carbogen is a gaseous mixture of from about 1% to about 50% CO₂ with the balance being O₂, with no specific anticancer effects of its own. Thus, combining carbogen with orally administered nicotinamide is believed to suppress the transient closure of small blood vessels and increase oxygenation of the tumor. (Robinson, et al., Br. J. Cancer (2000) 82: 2007-2014; Abstract attached hereto as Exhibit A).

The only cancerostatic or immunosuppressive agent disclosed in Hoskin is the radiation, which is not a chemotherapeutic agent of any kind, let alone a compound of formula I. It is respectfully submitted that Hoskin is essentially unrelated to the claimed subject matter.

Further, it is respectfully submitted that by preventing the closure of small blood vessels, nicotinamide actually enhances the vitality and metastatic potential of tumors by increasing tumor oxygenation (See Exhibit A, Abstract, lines 7-9). Therefore, Hoskin's use of nicotinamide as a sensitizing agent for radiation therapy is, too distinct from that disclosed and claimed in the subject application. Accordingly, persons of ordinary skill in the art would not interpret Hoskin as providing the requisite motivation to combine nicotinamide with compounds of formula I as disclosed in WO '397. Therefore, this combination of references is not sufficient to establish a *prima facie* case of obviousness.

Furthermore, the teachings of Exhibit A cast substantial doubt on nicotinamide's effectiveness as a sensitizing agent during radiation therapy, which is nicotinamide's

most well-known utility in oncology. Therefore, with nicotinamide's classic utility as a sensitizer during radiation treatment being in doubt, it is highly unlikely that persons of ordinary skill in the art would have interpreted Hoskin as establishing an even broader utility for nicotinamide as a chemosensitizing agent.

Accordingly, it is respectfully requested that the rejection based on the combined teachings and suggestions of WO '397 and Hoskin et al., be withdrawn.

Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over WO'397 in view of Olsson et al., (British Journal of Cancer, 1996, vol. 74, pages 368-373). The Office Action alleges that WO '397 discloses compounds encompassed by Formula I of the instant claims. More specifically the Office Action alleges that it teaches pharmaceutical compositions comprising a compound of Formula (I), e.g., N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide. It admits that it does not teach a compound having vitamin PP activity, e.g., a compound of Formulae II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va and Vb. However, the Office Action alleges that Olsson et al. encompass the instantly elected nicotinamide. The Office Action alleges that motivation is provided in Olsson by the disclosure therein that nicotinamide induces DNA damage and delays DNA repair when administered to mice bearing an immunogenic sarcoma.

Olsson teaches that nicotinamide induces DNA damage and repair when administered to mice inoculated with adenotype 12 virus-induced mouse sarcoma A12B3 and sarcoma F (Abstract). Administration of between 100 and 1000 mg/kg nicotinamide causes a high level of in vivo DNA strand breaks in tumors and in normal tissues in mice

bearing the immunogenic sarcoma A12B3. Nicotinamide also delayed the repair process of DNA strand breaks (Abstract).

It is respectfully submitted that the fact that Olsson discloses that nicotinamide induces DNA damage and delays DNA repair does not teach or suggest that nicotinamide, when combined with a cancerostatic or immunosuppressive agent, could reduce the side effects of the cancerostatic or immunosuppressive agent. It is further respectfully submitted that Olsson clearly teaches away from the use of nicotinamide by the following statements: "In addition, it should also be considered that high doses of NAM might cause considerable complications to normal tissue in tumour-bearing individual" (Summary) and "The potential of NAM as a radiosensitizer is currently being evaluated in several clinical trials (Kaanders et al., 1995). However, there have been a number of disturbing side-effects reported in the cancer patients receiving therapeutic doses of NAM (ESTRO, 1994; van der Maazen et al., 1995" (page 368, last line of left column through line 13 of right column). Therefore, Olsson provides abundant incentive to one of ordinary skill in the art not to use nicotinamide (NAM). Accordingly, in view of Olsson's warnings, it would be counterintuitive at best, to combine nicotinamide with a chemotherapy agent in order to reduce the side effects of the chemotherapy agent.

It is further respectfully submitted that persons of ordinary skill in the art readily appreciate that Olsson's disclosure that nicotinamide induces DNA damage and delays DNA repair in tumor cells runs contrary to the purpose of providing a cancerostatic composition. This is because it is known that an enhancement of DNA damage accompanied by a decreased ability to repair that damage is known to enhance the rate by which normal cells progress to cancer cells.

The disclosure in Olsson that nicotinamide induces DNA damage and delays DNA repair does not in and of itself, provide the necessary motivation to one skilled in the art to predict that combining nicotinamide with a cancerostatic or immunosuppressive agent would be therapeutically beneficial. As indicated hereinabove, Olsson teaches away from combining it with the primary reference.

It is therefore, respectfully submitted that combining the teachings of WO '397 with Olsson et al., does not provide a reasonable expectation of success to develop the cancerostatic compositions encompassed by the claims. Therefore, this combination of references is not sufficient to establish a *prima facie* case of obviousness.

As described above with respect to the Hoskin reference, it is noted that subsequent to the publication of Hoskin and Olsson, the results of another study were published (see Robinson, et al., Abstract attached, lines 8-9) (Exhibit A). These results cast substantial doubt on nicotinamide's effectiveness as a sensitizing agent during radiation therapy, which is nicotinamide's most well-known utility in oncology. Therefore, with nicotinamide's classic utility as a sensitizer during radiation treatment being in doubt, it is highly unlikely that persons of ordinary skill in the art would have interpreted Hoskin as establishing an even broader utility for nicotinamide as a chemosensitizing agent.

Accordingly, it is respectfully requested that the rejection based on the combined teachings and suggestions of WO '397 and Olsson et al., be withdrawn.

Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/48397 (Published December 24, 1997) (prior art of record) in view of Pero (USP No. 5,340,565).

The Office Action alleges that the WO '397 reference discloses compounds that are components of the pharmaceutical composition of the instant claims. The Office Action specifically alleges that the claimed pharmaceutical composition comprises a compound of Formula (I), e.g., N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide. It admits that it does not disclose a compound having vitamin PP activity according to Formula V. However, the Office Action concedes that WO '397 does not explicitly teach the specific combination of a compound of Formula (I) (e.g., N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide) and a vitamin PP active agent (e.g., nicotinamide) as recited in the instant claims.

The Office Action alleges that Pero teaches methods of inhibiting or killing tumor or cancer cells in a patient comprising administering "a chemotherapeutic agent" in combination with nicotinamide and an oxidative stressing agent (see claim 6 of Pero). The Office Action further alleges that nicotinamide has allegedly been shown to be an effective sensitizer of the cytotoxic action induced by radiation therapy and cancer chemotherapeutic drugs (col. 2, lines 21-46). It is further alleged that, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising a compound of Formula (I) as taught in WO 397 and nicotinamide as taught in Pero.

Applicants respectfully disagree and submit that establishing a prima facie case of obviousness, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. MPEP 2141.02(VI) (*citing W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)). Accordingly, when properly considered in its

entirety, Pero does not provide persons of ordinary skill in the art a reasonable expectation of success of arriving at the claimed combination.

With respect to the chemotherapeutic agents encompassed by Pero's teaching and Pero's claim 6, it is explicitly stated that chemotherapeutic agents of interest are limited to those that having cytotoxic effects resulting from the chemotherapeutic agents modulation of the catalytic activity of the enzyme adenosine diphosphate ribosyl transferase (ADPRT) (col. 1, lines 57-63). There is no teaching directed to other classes of chemotherapeutic agents other than ADPRT targeting compounds. Thus, the combination described in Pero's claim 6 does not encompass the claimed subject matter of the instant application. Further, there is no disclosure in the subject specification of the desirability of employing compounds that result in oxidative stress. Thus, absent a teaching or scientific rationale suggesting that Pero's combination of claim 6 is effective in the absence of the oxidizing stress agent, persons of ordinary skill in the art would not have been motivated to specifically combine the cancerostatic compound of WO' 397 with nicotinamide.

With respect to nicotinamide, it is respectfully suggested that a more critical review of Pero's comments are warranted. In brief, Pero merely provides a research scheme for creating a hypothetical class of compounds that are similar to nicotinamide, i.e., nicotinamide derivatives, not nicotinamide *per se*, and possess chemosensitizing properties. The purpose is apparently to take advantage of a nicotinamide transporter which has high affinity, thereby requiring a smaller dose of the hypothetical compound. In addition, the derivative would not be rapidly metabolized as is nicotinamide. See col. 2, lines 53-55.

Thus, what Pero hypothesizes is that nicotinamide derivatives or analogues would compete for the nicotinamide transporter and modulate ADPRT, thereby rendering the hypothetical analogues effective sensitizers of radio- and chemotherapies at non-toxic low doses," (col. 2, lines 58-62).

In view of the highly speculative nature of Pero's suggestion, and what is known in the art, persons of ordinary skill in the art would not reasonably expect that nicotinamide is effective as a chemosensitizer of chemotherapeutic agents. It is respectfully brought to the Examiner's attention that nicotinamide's utility in anticancer therapy has been limited to its role as a sensitizer of radiation therapy, not chemotherapy. The Office Action apparently cites Pero to bridge this gap in nicotinamide's known properties by attempting to conceptually link the utility of nicotinamide with other alleged chemosensitizing agents such as the xanthines, theophylline, purine analogues (col. 2, lines 47-48), and the compound metoclopramide (see Pero, Table I and Fig. 1). However, in the absence of evidence supporting such a role for nicotinamide it is respectfully submitted that this reasoning fails to establish that nicotinamide is an effective chemosensitizing agent.

The Examiner's attention is directed to the structural formula of nicotinamide (Exhibit B), and to note that nicotinamide is in a class of compounds that are structurally distinct from xanthine (Exhibit C), theophylline (Exhibit D), purine (Exhibit E), and metoclopramide (Exhibit F). Further, according to the Federal Circuit, these distinctions are sufficient to rebut any presumption that nicotinamide has similar utility and functionality to these compounds based on solely structural similarity. See, In re Mayne 41 USPQ2d 1451, 1454 (Fed. Cir. 1997). Accordingly, Pero's rationale for

nicotinamide's use as a chemosensitizing agent during chemotherapy is speculative at best and runs counter to the controlling case law on the subject.

Therefore, a critical review of Pero in its entirety would not provide persons of ordinary skill in the art a reasonable expectation of success in combining nicotinamide and a compound of WO '397.

Therefore, persons of ordinary skill in the art reading Pero in its entirety would not obtain a reasonable expectation of success that nicotinamide can be co-administered with just any chemotherapeutic agent, e.g., one from WO '397, and be an effective chemosensitizing agent, as well as mitigate the side effects of chemotherapy.

As discussed in relation to the Hoskin and Olsson references, it is noted that subsequent to the publication of Pero, the results of another study (see Robinson, et al., Abstract attached, lines 8-9) (Exhibit A) were published. These results cast substantial doubt on nicotinamide's effectiveness as a sensitizing agent during radiation therapy, which is nicotinamide's most well-known utility in oncology. Therefore, with nicotinamide's classic utility as a sensitizer during radiation treatment being in doubt, it is highly unlikely that persons of ordinary skill in the art would have interpreted Pero's speculative and hypothetical comments as establishing an even broader utility for nicotinamide as a chemosensitizing agent.

In conclusion, Applicants respectfully submit that combining the teachings of WO '397 with Pero does not provide persons of ordinary skill in the art a reasonable expectation of developing a combination of chemotherapeutic agent and nicotinamide as encompassed by the claims.

Accordingly, withdrawal of the rejection under § 103(a) is respectfully requested.

In view of the Amendments to the Claims and the Remarks herein, it is respectfully submitted that the present case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Mark J. Cohen". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Mark J. Cohen
Registration No. 32,211

Scully, Scott, Murphy & Presser, P.C.
400 Garden City Plaza, Suite 300
Garden City, NY 11530-0299
(516) 742-4343
MJC/TG:ab

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